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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,167	02/27/2002	James L. Holloway	99-29C1	3854

7590 01/28/2004

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,167	HOLLOWAY ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/27/02; 11/28/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 14-43* is/are pending in the application.

4a) Of the above claim(s) *15 and 17-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/24/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply.*

DETAILED ACTION

1. Claims 1-8, and 14-43 are pending.

2. Applicant's election with traverse of Group I, Claims 1-13 and 16 (now claims 1-8, 14 and 16) drawn to a polypeptide, filed 11/28/03, is acknowledged. The traversal is on the grounds that (1) a separate examination of these claims in these twenty seven groups would require substantial duplication of work on the part of the Office and it also would place an undue burden by requiring payment of twenty six separate filing fee for examination of the nonelected claims. Upon reconsideration, Groups 2-3 claim 14 drawn to polypeptide has been rejoined with Group I. However, claims 15 (fusion protein), claims 17-20 (antibody and method of making said antibody), claim 21 (anti-idiotypic antibody), claims 22-43 (polynucleotide, host cell, and method of making polypeptide) differ with respect to their binding specificity, structure and physiochemical properties. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter. Further, even though in some cases the classification is shared, a different field of search would be required based upon the structurally distinct products recited and the various methods comprising the distinct method steps. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention. Therefore, the requirement of Group 1 (now claims 1-8, 14 and 16) and Groups 4-27 is still deemed proper and is therefore made FINAL.

3. Claims 15, and 17-43 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-8, 14 and 16, drawn to polypeptide are being acted upon in this Office Action.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosure.

This application fails to comply with the sequence rules because SEQ ID NO is required on page 8, line 4. Appropriate correction is required.

6. The disclosure is objected to because incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 64, line 25 and page 65, line 13 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database.

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-8, 14 and 16 are rejected under 35 U.S.C. 101 as the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Applicant is directed to the Final Utility Guidelines, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999. In keeping with the revised utility guidelines and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific, credible and/or substantial use.

The specification discloses only a human zacrp4 polypeptide comprising SEQ ID NO: 2 wherein the polypeptide has the aromatic motifs within the first and second C1q domains of zacrp4. The C1q1 corresponds to amino acid residues 50-134 of SEQ ID NO: 2, and C1q2 corresponds to amino acid residues 203-286 of SEQ ID NO: 2 and the aromatic residues within the first C1q domain is from amino acid residues 50 to 80 of SEQ ID NO: 2. The aromatic motif within the second C1q2 domain is from amino acid residues 203 to 233 of SEQ ID NO: 2. The azcrp4 mRNA is expressed in ovarian and testis tissues (page 47, line 11) and in brain tissue (page 48, line 15). The specification speculates the claimed polypeptide may modulate hormones, hormone receptors, growth factors, or cell-cell interactions, of the reproductive

cascade or may be involved in oocyte or ovarian development, sperm or testis development, and would be useful as markers for cancer of reproductive organs and as therapeutic agents for hormone-dependent cancers, by inhibiting hormone-dependent growth and/or development of tumor cells (page 49) or may be used in the analysis of energy efficiency of a mammal (see pages 51), or may be evaluated for anti-microbial properties. Applicant asserts specific utilities for the claimed invention (use of the protein to make antibodies, to diagnose diseases with tissue expression of ZACRP4, and to identify antagonist of ZACRP4.

However, the disclosed use of isolated human zacrp4 polypeptide does not have a substantial or a well-established utility because the claimed polypeptide is not supported by a specific asserted utility. The disclosed use(s) such as making antibody and antagonist using of the claimed polypeptide is not specific and is generally applicable to any polypeptide. The disclosed use(s) such as diagnose disease with tissue that expressed ZACRP4 is not specific because until the specific disease affected by ZACRP4 has been identified, the diagnose use is merely an invitation for further experimentation.

Further, the asserted utilities are premised on the limited similarity of the disclosed full-length protein (SEQ ID NO: 2) to prior art protein ACRP30. The specification discloses ZACRP4, an adipocyte secreted protein, has 35 % identity to human adipocyte secreted protein ACRP30 (See page 12, line 37 bridging page 13, line 1). Clearly, 37% identity means 63 % differences. There is no recognition in the art that sequence identity predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art at the time the invention was made to believe said identity gives a credible use to the claimed protein. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al.*,(PTO 1449), of record, teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.,* teaches further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet *et al.*, (PTO 1449), teaches that a single Glu to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell

anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, paragraph bridging columns in particular). Attwood *et al.*, (PTO 1449), teaches that protein function is context-dependent; the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable and knowing structure alone will not inherently tell us function (See figure, entire document).

Note that while the specification produces the full-length protein recombinantly, no biological activity is established for the full-length protein or any of the claimed fragments thereof. The asserted function for zacrp4 based on homology, as disclosed in the specification, includes cell to cell communication (See page 47, line 4), spermatogenesis (See page 47, line 12), chemotaxis (See page 47), oogenesis (See page 48), regulation of reproductive function in male and females by feedback inhibition of the hypothalomus and anterior pituitary, modulator hormones associated with reproductive cascade (page 48), energy regulation (pages 49, 51), neural cell migration (page 52), host defense involving complement C1q (page 53-54), cell proliferation and/or differentiation (page 54-55), tissue remodeling (page 56), inflammation involving complement C1q, and wound healing (page 57-58). However, neither the specification nor the prior art teaches that the C1q related polypeptide such as ACRP30 actually has complement C1q activity nor that an increase or decrease expression of zacrp4 in instant application is actually associated with any disease. Further, mRNA expression (transcription) does not equal to protein expression (translation) in the tissue such as ovarian, testis and brain tissues. The specification is silent with respect to whether the full-length polypeptide has any specific functional or biological activity.

As such, further research would be required to identify or reasonably confirm a "real world" context of use. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved would be required. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-8, 14 and 16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Further, the term "comprising" is open-ended. It expands the amino acid residues 17-329 or 17-159 or 160-328 or 1-16 of SEQ ID NO: 2 to include additional undisclosed amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added and whether the resulting polypeptide maintain the same structure and function as SEQ ID NO: 2. Further, there is no working example demonstrating that the claimed polypeptide of SEQ ID NO: 2 or the modified undisclosed polypeptide has any specific function and/or activity.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the lack of guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 2 that after modification will retain both structure and have similar function is unpredictable. For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

11. Claims 1-8, 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any isolated polypeptide as set forth in claims 1-8, 14 and 16 for treating any disease.

The specification discloses only a human zacrp4 polypeptide comprising SEQ ID NO: 2 wherein the polypeptide has the aromatic motifs within the first and second C1q domains of zacrp4. The C1q1 corresponds to amino acid residues 50-134 of SEQ ID NO: 2, and C1q2 corresponds to amino acid residues 203-286 of SEQ ID NO: 2 and the aromatic residues within the first C1q domain is from amino acid residues 50 to 80 of SEQ ID NO: 2. The aromatic motif within the second C1q2 domain is from amino acid residues 203 to 233 of SEQ ID NO: 2. The

azcrp4 mRNA is expressed in ovarian and testis tissues (page 47, line 11) and in brain tissue (page 48, line 15).

With the exception of the specific polypeptide comprising SEQ ID NO: 2, there is insufficient written description about the structure associated with function of any isolated polypeptide "comprising" amino acid residues 17-329 of SEQ ID NO: 2, or any polypeptide has a first C1q domain "comprises" amino acid residues 17-159 of SEQ ID NO: 2, or a second C1q domain "comprises" amino acid residues 160-328 of SEQ ID NO: 2 because the term "comprising" or "comprises" is open-ended. It expands the amino acid residues 17-329 of SEQ ID NO: 2 or the amino acid residues 17-159 of SEQ ID NO: 2 or the amino acid residues 160-328 of SEQ ID NO: 2 to include additional undisclosed amino acids at either or both ends. There is inadequate written description about the undisclosed amino acids in the claimed polypeptide. Further, the specification discloses only one human polypeptide comprising SEQ ID NO: 2. Given the lack of a written description of *any* additional representative species of polypeptide having extra amino acids at either or both ends of SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "first C1q domain" in claim 3 is indefinite and ambiguous because the "first C1q domain" has been designated for SEQ ID NO: 3 in claim 2. Further, it is not clear whether the amino acid residues 17-159 of SEQ ID NO: 2 is part of the C1q domain of SEQ ID NO: 3. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

16. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The IFW official Fax number is (703) 872-9306.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
January 26, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)	
	Examiner Phuong N. Huynh	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: SEQ ID NO is required for page 8 line 4.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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